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(54) Title: ORAL PHARMACEUTICAL COMPOSITION CONTAINING A COMBINAITION OF PPARα AND A HMG-COA REDUCTASE INHIBITOR

(57) Abstract: Oral pharmaceutical composition containing, in the same pharmaceutical form, effective amounts of a HMG-CoA reductase inhibitor derivative and of PPARα, especially fenofibrate. Also described id the use of some inactive ingredients which allow to improve the dissolution and/or bioavailability of the drugs from the said composition.

Oral Pharmaceutical Composition Containing a Combination of PPARα and a HMG-CoA reductase inhibitor

ABSTRACT

Oral pharmaceutical composition containing, in the same pharmaceutical form, effective amounts of a HMG-CoA reductase inhibitor derivative and of a PPARα, especially fenofibrate. Also described is the use of some inactive ingredients which allow to improve the dissolution and/or bioavailability of the drugs from the said composition.

BACKGROUND OF THE INVENTION

Hypercholesterolaemia plays a crucial role in the development of atherosclerosis diseases in general and coronary heart disease in particular. The risk of progression of the atherosclerosis process to coronary heart diseases increases progressively with increasing levels of total serum cholesterol or low density lipoproteins (LDL) cholesterol at both the individual and the population level.

The HMG-CoA reductase inhibitors are reversible inhibitors of the microsomal enzyme HMG-CoA reductase, which converts HMG-CoA to mevalonate. This is an early rate-limiting step in cholesterol biosynthesis.

Inhibition of HMG-CoA reductase by HMG-CoA reductase inhibitors decreases intracellular cholesterol biosynthesis, which then leads to transcriptionnally upregulated production of microsomal HMG-CoA reductase at cell surface LDL receptors.

Subsequently, additional cholesterol is provided to the cell by de novo synthesis and by receptor-mediated uptake of LDL-cholesterol from the blood. This resets intracellular cholesterol homeostasis in extrahepatic

tissues, but has little effect on the overall cholesterol balance (Clin. Pharmacokinet. 1997, May, 32(5), 403-425).

The main HMG-CoA reductase inhibitors currently used in therapeutics are: pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. simvastatin, lovastatin and pravastatin are derived from fungi (14,15).

simvastatin reductase inhibitor is a clinically modified 2,2-dimethyl-butyrate analogue of lovastatin.

Fibrates are old hypolipidemic drugs with pleitropic effects on lipid metabolism. Their intimate molecular mechanisms of action have been mysterious for a long time. Recently, it has been shown that the pharmacological effect of fibrates depends on their binding to "Peroxisome Proliferator Activated Receptor alpha" (PPAR alpha). The binding of fibrates to PPAR induces the activation of the inhibition of multiple genes involved in lipid metabolism through the binding of the activated PPAR alpha to "Peroxisome Proliferator Response Element" (PPRE) located in the gene promoters. Furthermore, it was recently demonstrated that fibrates are potent antiinflammatory molecules through an indirect modulation of the nuclear-factor-Kappa B activity.

Fenofibrate or P-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 100 to 300 mg which is administered in two or three doses. Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

It has been demonstrated that the combination of a HMG-CoA reductase inhibitor and fenofibrate (administered in two separate dosage forms) was better tolerated and as efficient as a higher dose of the HMG-CoA reductase inhibitor derivative. The main disadvantage of this double administration is that it complicates the posology for the patients and hence it increases the risk of mistakes or omissions in the intake of drugs. The patient's compliance is then decreased.

Consequently, there is still a need for patients suffering from hypercholesterolemia and/or lipidemia to dispose of a pharmaceutical dosage form containing effective amounts of at least one HMG-CoA reductase inhibitor derivative and of fenofibrate and allowing to obtain a good bioavailability of both drugs.

Some patents describing association of hypolipidemiant agents are already described. For instance, US patent 6,180,660 describes methods for preventing or reducing the risk of a first occurrence of a cardiovascular event using an HMG-CoA reductase inhibitor alone or in combination with another lipid altering agent. Subjects to be treated are those having an average serum total cholesterol level, an average to mildly elevated serum low-density lipoprotein cholesterol level, and a below average serum high-density lipoprotein cholesterol level, with no history of clinically evident coronary disease.

The US Patent 6,264,938 relates to methods for treating hypercholesterolemia and atherosclerosis, and reducing serum cholesterol in a mammal. The methods of the invention comprise administering to a mammal a first amount of a bile acid sequestrant compound which is an unsubstituted polydiallylamine polymer and a second amount of an HMG CoA reductase inhibitor compound. The first and second amounts together comprise a therapeutically effective amount. The invention further relates to pharmaceutical compositions useful for the treatment of hypercholesterolemia and atherosclerosis, and for reducing cholesterol.

The WO 01/37831 describes a pharmaceutical combination comprising separate dosage form in a common blister card of an inhibitor of the HMG-CoA reductase and a fibric acid derivative useful in the treatment at different ways of dyslipidemia of diabetics and non-diabetics.

US Patent 5,545,628 describes an advantageous oral pharmaceutical composition containing fenofibrate while the patent PCT/BE 01/00098 describes an advantageous semi-solid oral pharmaceutical composition containing an HMG-CoA reductase.

Not described is an oral semi-solid pharmaceutical composition containing, in the same pharmaceutical form, a combination of an effective amount of a HMG-CoA reductase inhibitor derivative together with an effective amount of a PPARα agent, especially fenofibrate.

SUMMARY OF THE INVENTION

The present invention relates to an oral pharmaceutical composition, containing a combination of effective amounts of at least one HMG-CoA reductase inhibitor derivative and of PPARα agent, especially fenofibrate, in the same dosage form, allowing to obtain a high bioavailability of all drugs. The invention also relates to a process for manufacturing the same.

DETAILED DESCRIPTION OF THE INVENTION

It is an object of the present invention to disclose a pharmaceutical dosage form containing PPARα agent, especially fenofibrate, and at least a HMG-CoA reductase inhibitor of the statin family.

It is another object of the present invention to disclose a pharmaceutical dosage form containing PPARα agent, especially fenofibrate, and at least a HMG-CoA reductase inhibitor contained in a capsule or a tablet.

Another object of the present invention is to disclose a pharmaceutical dosage form containing PPARα agent, especially fenofibrate, and at least a HMG-CoA reductase inhibitor with increased bioavailability for both the PPARα agent, especially fenofibrate, and all the HMG-CoA reductase inhibitor.

Also an object of the present invention is to disclose a pharmaceutical dosage form containing PPARα agent, especially fenofibrate, and at least a HMG-CoA reductase inhibitor from which at least the PPARα agent, especially fenofibrate, has an increased bioavailability.

Also an object of the present invention is to disclose a pharmaceutical dosage form containing PPARα agent, especially fenofibrate, and at least a HMG-CoA reductase inhibitor from which at least one of the HMG-CoA reductase inhibitors have an increased bioavailability.

The formulation contains advantageously at least one hydrophilic agent (HLB > 10) and/or one or more stabilizing agent(s) e.g. one or more antioxidant or preservative agent or a combination of both preservative and antioxidant agents.

According to the invention, a pharmaceutical composition useful for administration to a mammal comprises in a same dosage form an effective amount of at least one peroxisome proliferator activated agent (PPARα), an effective amount of at least one HMG-CoA reductase inhibitor derivative of the statin family, and at least one polyglycolized glyceride or another derivative of glyceride.

Preferably, the composition comprises at least one peroxisome proliferator activated agent (PPARα) under the form of semi-solid composition (containing at least one polyglycolized glyceride or another derivative of glyceride) and at least one HMG-CoA reductase inhibitor derivative of the statin family under the form of a coated tablet, both the semi-solid form and the tablet being filled in one single pharmaceutically acceptable capsule

Preferably, the composition further comprises at least one hydrophilic disintegrating agent. Examples of disintegrating agents are sodium starch glycolate, sodium croscarmellose, crospovidone, starch, colloidal silicone dioxide or another pharmaceutically accepted disintegrating agent and combinations thereof, sodium starch glycolate being preferred .

In the composition of the invention, the PPARα agent is advantageously a compound of the fibrate family, preferably a compound selected from the group consisting of fenofibrate, ciprofibrate, clofibrate, gemfibrozil, bezafibrate and combinations thereof. Especially, the PPARα agent is fenofibrate.

The pharmaceutical composition of the invention is preferably in a form suitable for the oral administration of the active agents.

The polyglycolised glyceride has advantageously an HLB balance above 10, preferably above 11, most preferably above 12.

According to an embodiment, the melting point of the said composition is below 90°C, preferably below 80°C, most preferably below 70°C.

The pharmaceutical composition of the invention contains advantageously one or more antioxidant and/or preservative agent(s), such as a vitamin E derivative and/or a methoxyphenol derivative and/or a combination thereof.

The pharmaceutical composition of invention contains advantageously a wetting agent.

The composition of the invention further contains advantageously a polyethylene glycol or a mix of polyethylene glycol with different molecular

mass; and/or a suspension stabilizer, such as a cellulose derivative, hydropropylcellulose.

The composition of the invention is adapted for the administration of specific amount of active agent per dose. Advantageously, the amount of PPARα, preferably fenofibrate, per dose is between 30 and 400 mg, while the amount of statin per dose is between 5 and 100mg, the amount of statin per dose being preferably lower than the amount of PPARα per dose, most preferably comprised between 0.01 and 0.5 times the amount of PPARα per dose.

The composition of the invention is for example filled in hard gelatine capsules, hypromellose capsules or in other pharmaceutically acceptable capsules.

According to a preferred detail of the composition, the composition is with the proviso that the PPARα, preferably fenofibrate, is not co-micronized, and/or, preferably and, with the proviso that the statin is not co-micronized.

According to preferred embodiments, the weight ratio PPAR agent + statin/hydrophilic disintegrating agent is comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, more preferably between 6 and 25, such as 8, 10, 12, 14, etc.

According to a further detail of a preferred embodiment, the weight ratio PPAR + statin agent/polyglycolized glyceride(s) is comprised between 10 and 0.1, advantageously between 5 and 0.2, preferably lower than 1, more preferably between 0.8 and 0.3, such as about 0.8, 0.7, 0.6, 0.5, 0.4.

For example, at least one HMG-CoA reductase inhibitor derivative of the statin family is advantageously selected from the group consisting of pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. simvastatin, lovastatin, pravastatin and mixtures thereof.

The pharmaceutical composition of the invention advantageously further contains a polyethyleneglycol derivative (PEG). The amount of PEG is advantageously comprised between 0.2 and 5 times the amount of stain

present in the composition, preferably between 0.5 and 2 times the amount of statin present in the composition.

According to a specific embodiment, the composition contains one or more antioxidant and/or preservative agent(s), one polyethylene derivative, and one hydrophilic wetting agent.

The semi-solid composition may be a suspension, an emulsion or a micro-emulsion. The HMG-CoA reductase inhibitor agent and the fibric acid derivative may be partially or totally dissolved in the semi-solid matrix formed by the excipients.

The advantages of the semi-solid formulations are multiple for HMG-CoA reductase inhibitors: protection of the active ingredient from air and humidity, possibility of increasing the dissolution rate of the molecule and hence of bioavailability, diminution of the risk of contamination of the operator, diminution of the risk of cross contamination, no possibility of demixing under the effect of vibrational mixing during manufacturing process, facility of the production process. The choice of the nature of the formulation of course influenced the stability of the pharmaceutical form and the bioavailability of the drug contained in it. Generally, a maximum bioavailability is achieved by preparing and keeping the drug in the amorphous/solubilized state in a solid dispersion or in a lipid-based formulation. For these systems, the barrier we are avoiding is the compound « washing-out » of solution to a large extent into a insoluble crystalline form during the dissolution/release step in vivo.

These systems may consist of suspension, emulsion, microemulsion, self-emulsifying drug delivery systems (SEDDS) or self-emulsifying microemulsion drug delivery system (SMEDDS).

Microemulsions have the added advantage over suspensions such as emulsions and dispersions since thermodynamically they are more stable, that they can be manufactured with little energy input and have generally a longer shelf-life.

The formation of oil-in-water (O/W) and water-in-oil (W/O) microemulsions usually involves a combination of 3-5 basic compounds i.e. oil, surfactant, cosurfactant, water and electrolytes. The challenge is to select for a particular application oil(s) and surfactant(s) that are acceptable from a toxicological perspective and that allow to obtain a high bioavailability of the drug.

The assessment of the quality of semi-solid lipid based formulations is quite difficult since the in vitro dissolution test is of little help. Indeed, the in vitro/in vivo correlation between dissolution and bioavailability is very poor for this kind of formulation. Other analytical tools are available to the formulator to try to predict the in vivo bioavailability of isotretinoin from various formulations like the CACO-2 cells model, the assessment of the percentage of drug dissolved in the formulation, differential scanning calorimetry, microscopy,...

Nevertheless, none of them present a guarantee of in vitro / in vivo correlation and ultimately only pharmacokinetic studies on human subjects are reliable to assess the bioavailabiltiy of the drug.

Advantageously, the melting point of the final composition will be below 80°C, preferably below 60°C.

Advantageously, an emulsifier may be added (e.g distilled monoglycerides, Myverol® , Gillco, US) to the formulation in order to increase the solubilization of the HMG-CoA reductase inhibitor.

Advantageously, the oral pharmaceutical composition may contain a solubilizing agent. This solubilizing agent is advantageously water and HCl soluble. An example of this kind. of solubilizing is diethylene glycol monoethyl ether (Transcutol®, Gattefossé).

Also advantageous for the stability and the bioavailability of the composition is the addition of an antioxidant agent such as either a Tocopherol

derivative like Tocopherol (Vitamine E), Tocopherol acetate, Vitamine E TPGS or a methylphenol derivative like butylhydroxyanisol (BHA) or butylhydroxytoluene (BHT).

The addition of a polymer able to control the recristallisation of the active ingredient may also be useful when the active ingredient is not completely dissolved in the semi-solid matrix.

The role of the polymer is (i) to stabilize the semi-solid formulation by increasing the viscosity of the composition and (ii) to avoid the growth of particles of active ingredient that are not solubilized (or formed during the cooling of the composition) by forming a matrix in the semi- solid composition.

Examples of such agents are cellulose derivatives such as hydroxypropylcellulose, hypromellose and methylcellulose.

A wetting agent may also be added advantageously to the said composition when a very fast release in needed. Example of such agents are Na croscarmellose, Na carboxymethylcellulose or reticulated povidone. The effect of the wetting agent is strongly dependent on the nature of the active ingredient and on the nature of the semi-solid matrix.

Process for manufacturing the said pharmaceutical composition.

One of the advantages of the invention relates to the easiness of the manufacturing process of the medication and the rapidity and easiness of the pharmaceutical composition.

Briefly, the inactive ingredients are used as molten together. In an adequate tank the active ingredient is added to the molten mass and once the solution mass is homogenous, the molten is filled into pharmaceutically acceptable capsules e.g. hard gelatin capsules or hypromellose capsules. The capsules are then cooled and thereafter adequately packaged.

Examples of formulations

Example 1

Ingredient	mg/capsule		
	F1	F2	F3
Simvastatin	20	15	12
Fenofibrate	200	160	160
Gelucire 44/14®	350	300	400
Vit E TPGS	20	30	30
Polyethyleneglycol 6000	30	20	30
Butylhydroxyanisole	0.08	0.04	0.08
Propyl gallate	--	0.04	--

Example 2

Ingredient	mg/capsule		
	F4	F5	F6
lovastatin	15	15	12
Fenofibrate	150	150	160
Gelucire 44/14®	--	350	--
Gelucire 50/13	350	--	400
PEG 6000	--	--	20
PEG 2000	--	20	10
Butylhydroxyanisole	0.04	--	0.04
Butylhydroxytoluene	0.04	0.08	0.04

Example 3

Ingredient	mg/capsule
semi-solid formulation	
	160
Fenofibrate	95
hydropropylcellullose	350
Gelucire 44/14®	60
PEG 6000	
uncoated tablet	12,5
	70
Pravastatin	15
Mannitol	11,5
Lactose	9
Microcrystalline cellulose	0.01
Sodium starch glycolate	2
butylhydroxyanisole	
Magnesium Stearate	
Coating of the tablet	
Absolute ethanol	36,46
Povidone	7,29
Talc	3,64
Triacetin	0,607
pro capsula una	

The example 3 hereinabove describes a composition corresponding to the present invention wherein the fenofibrate is formulated as a semi-solid formulation and the pravastatin as a coated tablet formulation, the fenofibrate and pravastatin formulations being filled as a single composition in one single hard gelatin capsule.

Example 4

Ingredient	mg/capsule		
	F7	F8	F9
pravastatin	30	40	25
Fenofibrate	160	200	160
Gelucire 44/14®	350	300	300
PEG 6000	20	20	30
Vit E TPGS	30	20	30
Sodium starch glycolate	20	10	20
Lactose	--	10	--
Butylhydroxyanisole	0.08	0.08	0.08
Hydroxypropylcellulose	--	--	100

In the present specification, the term "improved bioavailability" relates to the human bioavailability of the drug(s) in humans. The bioavailability of a drug is defined as the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes active at the site of action. The bioavailability is essentially quantified by the area under the plasma concentration curve (AUC) and the maximal plasma concentration (C_{max}). Consequently, an improved form of the invention presents a higher bioavailability (AUC and/or C_{max}), preferably a significantly higher bioavailability than the reference, namely the actually commercialized fenofibrate form or/and the actually commercialized HMG-CoA reductase form, the drug being taken via the oral route at the same dose. The preferred form of the invention presents a higher bioavailability (AUC and/or C_{max}), preferably a significantly higher bioavailability than the references which are respectively the actually commercialized form of fenofibrate and the actually commercialized form of HMG-CoA reductase inhibitor, when the products are taken via the oral route at the same dose. The improved bioavailability is for example improved of at least 10%,

advantageously of at least 15%, preferably of at least 20% with respect to the bioavailability of the reference.

The compositions of the various formulations F1 to F9 of examples 1 to 3 have been repeated, except that the fenofibrate has been replaced by ciprofibrate, clofibrate, gemfibrozil, bezafibrate, a combination of bezafibrate (50%) and fenofibrate (50%).

CLAIMS

1. A pharmaceutical composition useful for administration to a mammal, said composition comprising in a same dosage form an effective amount of at least one peroxisome proliferator activated agent (PPARα), an effective amount of at least one HMG-CoA reductase inhibitor derivative of the statin family, and at least one polyglycolized glyceride or another derivative of glyceride.
2. The pharmaceutical composition of claim 1, wherein the PPAR agent is contained in a semi-solid vehicle containing at least least one polyglycolized glyceride or another derivative of glyceride and the statin derivative is formulated as a tablet, both molecule's formulations being filled into one single pharmaceutically acceptable capsule
3. The pharmaceutical composition of claim 1, wherein the PPAR agent is contained in a semi-solid vehicle containing at least least one polyglycolized glyceride or another derivative of glyceride and the statin derivative is formulated as a coated tablet, both molecule's formulations being filled into one single pharmaceutically acceptable capsule
4. The pharmaceutical composition of claim 1, which comprises at least one hydrophilic disintegrating agent.
5. The pharmaceutical composition of claim 1, wherein the PPARα is a compound of the fibrate family, preferably a compound selected from the group consisting of fenofibrate, ciprofibrate, clofibrate, gemfibrozil, bezafibrate and combinations thereof.
6. The composition of claim 1, wherein the PPARα agent is fenofibrate.
7. The pharmaceutical composition of claim 1, wherein the said pharmaceutical composition is administered via the oral route.

8. The pharmaceutical composition of claim 7, wherein the polyglycolised glyceride has an HLB balance above 10, preferably above 11, most preferably above 12.
9. The pharmaceutical composition of claim 1, wherein the melting point of the said composition is below 90°C, preferably below 80°C, most preferably below 70°C.
10. The pharmaceutical composition of claim 1 containing one or more antioxidant and/or preservative agent(s).
11. The pharmaceutical composition of claim 8, wherein the antioxidant and/or preservative agent is a vitamin E derivative.
12. The pharmaceutical composition of claim 8, wherein the antioxidant and/or preservative agent is a methoxyphenol derivative.
13. The pharmaceutical composition of claim 8, where a combination of a vitamin E derivative and a methoxyphenol derivative is used as antioxidant and/or preservative agent.
14. The pharmaceutical composition of claim 1, wherein the composition contains a wetting agent.
15. The pharmaceutical composition of claim 2, wherein the disintegrating agent is sodium starch glycolate.
16. The composition of claim 2, wherein the disintegrating agent is sodium croscarmellose, crospovidone, starch, colloidal silicone dioxide or another pharmaceutically accepted disintegrating agent.
17. The composition of claim 1 further containing a polyethylene glycol or a mix of polyethylene glycol with different molecular mass.
18. The composition of claim 1, wherein a suspension stabilizer is added in the composition.
19. The composition of claim 16, wherein the suspension stabilizer is a cellulose derivative.
20. The composition of claim 16, wherein the suspension stabilizer is hydropropylcellulose.
21. The composition of claim 1, wherein the amount of PPARα, preferably fenofibrate, per dose is between 30 and 400 mg, while the

amount of statin per dose is between 5 and 100mg, the amount of statin per dose being preferably lower than the amount of PPARα per dose, most preferably comprised between 0.1 and 0.5 times the amount of PPARα per dose.

22. The composition of claim 1, wherein the composition is filled in hard gelatine capsules, hypromellose capsules or in other pharmaceutically acceptable capsules.

23. The composition of claim 1, which is with the proviso that the PPARα, preferably fenofibrate, is not co-micronized, and/or, preferably and, with the proviso that the statin is not co-micronized.

24. The composition of claim 1, in which the weight ratio PPAR agent + statin/hydrophilic disintegrating agent is comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, more preferably between 6 and 25.

25. The composition of claim 2, in which the weight ratio PPAR + statin agent/polyglycolized glyceride(s) is comprised between 10 and 0.1, advantageously between 5 and 0.2, preferably lower than 1, more preferably between 0.8 and 0.3.

26. The pharmaceutical composition of claim 1, wherein at least one HMG-CoA reductase inhibitor derivative of the statin family is selected from the group consisting of pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. simvastatin, lovastatin, pravastatin and mixtures thereof.

27. The pharmaceutical composition of claim 1, wherein the composition further contains a polyethyleneglycol derivative.

28. The pharmaceutical composition of claim 1, wherein the composition contains one or more antioxidant and/or preservative agent(s), one polyethylene derivative, and one hydrophilic wetting agent.

29. A method of treating hyperlipidemia and/or hypercholesterolemia in human in need thereof, which comprises administering orally substantially simultaneously, an effective amount of at least one

peroxisome proliferator activated agent (PPARα), an effective amount of at least one HMG-CoA reductase inhibitor derivative of the statin family, and at least one polyglycolized glyceride or another derivative of glyceride.

30. The method of claim 27, which comprises at least one hydrophilic disintegrating agent.

31. The method of claim 27, wherein the PPARα is a compound of the fibrate family, preferably a compound selected from the group consisting of fenofibrate, ciprofibrate, clofibrate, gemfibrozil, bezafibrate and combinations thereof.

32. The method of claim 27, wherein the PPARα agent is fenofibrate.

33. The method of claim 27, wherein at least one HMG-CoA reductase inhibitor derivative of the statin family is selected from the group consisting of pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. simvastatin, lovastatin, pravastatin and mixtures thereof.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/BE 02/00135

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P3/06 //(A61K45/06,31:215)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 455 042 A (E.R.SQUIBB & SONS) 6 November 1991 (1991-11-06) claims 1-4 page 3, line 31-34 page 3, line 49 -page 4, line 7 page 4, line 34-43 example 1 --- -/--	1-7,9, 10,14, 16,18, 19, 21-23, 26,28,29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2002	12/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 475 148 A (E.R.SQUIBB & SONS) 18 March 1992 (1992-03-18) claims 1,2,4-6,8-10 page 3, line 15-17 page 3, line 30-36 page 4, line 15-24 example 1	1-7,9, 10,14, 16,18, 19, 21-23, 26,28,29
X	WO 00 37078 A (BAYER) 29 June 2000 (2000-06-29) claims 1-9,11 page 3, line 28 -page 4, line 4 page 6, line 19 -page 7, line 14 examples 4,6	1-7,9, 10,14, 16, 18-23, 26,28,29
A	R.L.B.ELLEN, R.MCPHERSON: "Long-term efficacy and safety of fenofibrate and statin in the teatment of combined hyperlipidemia" AMERICAN JOURNAL OF CARDIOLOGY, vol. 81, no. 4A, 1998, pages 60B-65B, XP000925448 page 60B page 61B, column 1	1,5-7, 26,29
A	M.FARNIER, S.DEJAGER: "Effect of combined fluvastatin-fenofibrate therapy compared with fenofibrate monotherapy in severe primary hypercholesterolemia" AMERICAN JOURNAL OF CARDIOLOGY, vol. 85, no. 1, 2000, pages 53-57, XP001073750 page 53 page 54 page 56, column 2	1,5-7, 26,29

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE 02/00135

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 29-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 1-4, 7-30 and 33 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely:

"Peroxisome proliferator activated agent (PPAR-alpha)"

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely claims 5,6,31,32 and for the compounds cited in the examples, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 02/00135

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